REMARKS

Entry of the amendments is proper

A response to the Office Action of December 15, 2000 was previously filed on February 15, 2001. According to the Advisory Action of March 6, 2001 the amendments and arguments filed February 15, 2001 have overcome the rejections of claims 32 and 33 under 35 U.S.C. § 112, first and second paragraphs, and the rejections of claims 17 and 18 under 35 U.S.C. § 101 and § 112, first paragraph. However, these amendments were not deemed sufficient to overcome the remaining rejections of claims 17 and 18 for alleged lack of adequate written description under 35 U.S.C. § 112, first paragraph, and the rejections of claims 17 and 32 under 35 U.S.C. § 102(b) and § 103.

Claims 2-10 and 17-43 are pending in the application. Claims 2-10 have been canceled. Claims 19-31 and 34-43 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claim 17 has been amended to further clarify the intended subject matter of the claimed invention. No new matter has been added by these amendments. The present amendment does not introduce any new issues, and places the subject application in condition for allowance and/or simplifies issues for appeal. Therefore, entry of the amendment is proper and is respectfully requested..

Rejections under 35 U.S.C. § 112, first paragraph for alleged lack of written description:

The rejection of claims 17 and 18 under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description was maintained. The Examiner asserts that Appellants "have yet to define what specific amino acid should be designated as "biologically active" and "immunologically active" fragments. Applicants have yet to express where the biologically-activity [sic] resides in the claimed fragments." (Advisory Action, page 1.)

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled

> in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

In order to further clarify the intended subject matter of the claimed invention, the "fragment" language of independent claim 17 has been amended so that it now recites "a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment is imported into the inner mitochondrial membrane", and "an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active fragment comprises at least 10 contiguous amino acids of SEQ ID NO:1 and generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1."

Support for these amendments is found in the specification at page 46, line 24 through page 47, line 16, wherein the specification describes methods for determining the biological activity of HuTIM17 by assaying its import into the mitochondrial inner membrane, and at page 26, line 29 through page 27, line 1, wherein the specification states that "[i]t is preferred that the

peptides, fragments, or oligopeptides used to induce antibodies to HuTIM17 have an amino acid sequence consisting of at least five amino acids, and more preferably at least 10 amino acids."

The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, Figure 2. At, for example, pages 12, lines 9-20, the Specification describes the chemical and structural characteristics of the polypeptide of SEQ ID NO:1 (HuTIM17). The polypeptide and fragments thereof can be produced by either recombinant means (see, *e.g.*, the Specification at page 16, line 17 through page 17, line 13; and pages 18-22) or by chemical synthesis (see, *e.g.*, the Specification at page 17, lines 16-21; and page 24, lines 15-21).

Note that at page 6, lines 21-25, biologically active is defined as "a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule" and "immunologically active" is defined as "the capability of the natural, recombinant, or synthetic HuTIM17, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies." Specific binding is further defined at page 10, lines 15-21, as meaning that:

> . . . in reference to the interaction of an antibody and a protein or peptide, mean[s] that the interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) on the protein; in other words, the antibody is recognizing and binding to a specific protein structure rather than to proteins in general. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

Methods of producing specifically binding antibodies are described, for example, at pages 26-28. The specification indicates that "[i]t is preferred that the peptides, fragments, or oligopeptides used to induce antibodies to HuTIM17 have an amino acid sequence consisting of at least five amino acids, and more preferably at least 10 amino acids" (Specification, page 26, line 29 through page 27, line 1). See also pages 47-48 which describe the production of antibodies to fragments of HuTIM17, including the description of how to identify appropriate immunogenic sites of HuTIM17:

> The amino acid sequence deduced from SEQ ID NO:2 is analyzed using DNASTAR software (DNASTAR Inc) to determine regions of high immunogenicity, and a corresponding oligopolypeptide is synthesized and used to

> raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is described by Ausubel et al. (supra), and others. (Specification at page 47, lines 21-25)

Furthermore, as mentioned above, the Specification describes methods for determining the biological activity of HuTIM17 by assaying its import into the mitochondrial inner membrane, at pages 46-47. The localization of a membrane protein such as HuTIM17 depends in part upon the presence of transmembrane domains. The potential transmembrane domains of HuTIM17, polypeptide fragments comprising amino acids 16 to 34, 63 to 82, and 94 to 135 of SEQ ID NO:1 are described in the Specification at page 12, lines 15-17.

Given the "blueprint" provided by SEQ ID NO:1, and the detailed guidance set forth by the Specification, the structure of fragments of SEQ ID NO:1 is apparent and there is no need to explicitly list the sequences of the numerous possible fragments. Such a list would just needlessly clutter the Specification.

Thus the disclosure of the instant application satisfies the written description requirements under 35 U.S.C. § 112, first paragraph, based on the literal disclosure in the specification and what was known in the art at the time the application was filed. For at least these reasons, Applicants request withdrawal of the rejections.

Rejections under 35 U.S.C. §§ 102/103:

The rejections of claim 17 stands under 35 U.S.C. 102(b) as allegedly anticipated by various references including Accession Numbers P39515, Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991, and of claim 32 stands under 35 U.S.C. 103(a) as allegedly being unpatentable over the above references in view of Harlow and Lane, were maintained.

Applicants have pointed out in the previous response that the reference fragments, derived from yeast MIM17, would be no longer than six amino acid residues (see the alignment between yeast MIM17 (GI557267) and HuTIM17 as shown in Figure 2), and thus would lack the transmembrane domains required for successful insertion into the mitochondrial membrane. The Examiner has asserted that "these points are not recited in the claims, hence do not absolve the art

rejections of claims 17 and 32". The Examiner has further asserted that this statement "is Applicants' opinion and not an established fact", and that "[t]here is no fact pattern presented by Applicants that the referenced fragments would not inherently retain the activities as listed in the claims." (Advisory Action, page 1).

Applicants note that claim 17(c), as amended herein, now recites "a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment is imported into the inner mitochondrial membrane". Support for this amendment is found in the specification at page 46, line 24 through page 47, line 16, wherein the specification describes methods for determining the biological activity of HuTIM17 by assaying its import into the mitochondrial inner membrane. The claims as amended specifically incorporate the requirement that the claimed fragments can be imported into the inner mitochondrial membrane. Since the reference fragments, lacking transmembrane domains, cannot be successfully imported, they do not anticipate.

Applicants also respectfully point out that the requirements for transmembrane domains in membrane proteins are well known in the art, and are discussed in, for example, the enclosed reference, S.J. Singer, "The structure and insertion of integral proteins in membranes" Annu. Rev. Cell Biol. (1990) 6:247-296. As Singer discloses, "essentially all integral proteins known at present appear to be TM molecules" (page 267). The characteristic transmembrane domain is 15-25 hydrophobic amino acid residues in length (page 253), and in fact the mechanism of insertion into the membrane requires a hydrophobic stretch of at least about 20 amino acid residues (pages 272-273). The reference fragments would be at best six amino acids in length, and thus would be immediately recognized by one of skill in the art as simply being too short to serve as transmembrane domains. Since the ability to be inserted into a membrane is explicitly required of the claimed biologically active fragments, the reference fragments do not anticipate the claims.

The Examiner has further asserted that "in regards to immunological activity, four amino acids is defined as an epitope, thus immunologically active" (Advisory Action, pages 1-2). Applicants note that claim 17(d), as amended herein, now recites "an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active

fragment comprises at least 10 contiguous amino acids of SEQ ID NO:1 and generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1." Support for this amendment is found in the specification at page 26, line 29 through page 27, line 1, wherein the specification states that "[i]t is preferred that the peptides, fragments, or oligopeptides used to induce antibodies to HuTIM17 have an amino acid sequence consisting of at least five amino acids, and more preferably at least 10 amino acids." Since none of the references disclose fragments comprising at least 10 contiguous amino acids of SEQ ID NO:1, they do not anticipate the claims.

Thus the cited references do not disclose the claimed fragments having the recited activities, and therefore fail to anticipate claim 17. Nor are compositions comprising the fragments, as in claim 32, made obvious by the references in view of Harlow and Lane, since Harlow and Lane is a general reference on antibody methods and does not disclose the claimed fragments. The withdrawal of the rejections of claims 17 and 32 is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This form is enclosed in duplicate.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 17 has been amended as follows:

17. (Thrice Amended.) A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1,

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1,

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment is imported into the inner mitochondrial membrane [has translocase of inner mitochondrial membrane 17 activity], and

d) an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active fragment comprises at least 10 contiguous amino acids of SEQ ID NO:1 and generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1.